ECM-dependent HIF induction directs trophoblast stem cell fate via LIMK1-mediated cytoskeletal rearrangement.

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Public Summary:
The Hypoxia-inducible Factor (HIF) family of transcriptional regulators coordinates the expression of dozens of genes in response to oxygen deprivation. Mammalian development occurs in a hypoxic environment and HIF-null mice therefore die in utero due to multiple embryonic and placental defects. Mouse embryonic stem cells do not differentiate into placental cells; therefore, trophoblast stem cells (TSCs) are used to study mouse placental development. Consistent with a requirement for HIF activity during placental development in utero, TSCs derived from HIF-null mice exhibit severe differentiation defects and fail to form trophoblast giant cells (TGCs) in vitro. Interestingly, differentiating TSCs induce HIF activity independent of oxygen tension via unclear mechanisms. Here, we show that altering the extracellular matrix (ECM) composition upon which TSCs are cultured changes their differentiation potential from TGCs to multinucleated syncytiotropholasts (SynTs) and blocks oxygen-independent HIF induction. We further find that modulation of Mitogen Activated Protein Kinase Kinase-1/2 (MAP2K1/2, MEK-1/2) signaling by ECM composition is responsible for this effect. In the absence of ECM-dependent cues, hypoxia-signaling pathways activate this MAPK cascade to drive HIF induction and redirect TSC fate along the TGC lineage. In addition, we show that integrity of the microtubule and actin cytoskeleton is critical for TGC fate determination. HIF-2α ensures TSC cytoskeletal integrity and promotes invasive TGC formation by interacting with c-MYC to induce non-canonical expression of Lim domain kinase 1-an enzyme that regulates microtubule and actin stability, as well as cell invasion. Thus, we find that HIF can integrate positional and metabolic cues from within the TSC niche to regulate placental development by modulating the cellular cytoskeleton via non-canonical gene expression.

Scientific Abstract:
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